**SYNLETT Spotlight 311**

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research.

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**N,N’-Dimethyl Urea**

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**Introduction**

*N,N’*-Dimethyl urea (DMU) (1,3-dimethyl urea, methyl carbamide) is a colourless solid and a non-volatile, versatile and powerful reagent for the synthesis of nitrogen-containing heterocyclic compounds. It is used for the synthesis of caffeine, theophylline, pharmaceuticals, textile aids, herbicides, etc. It also finds application in metal-ion complexation, material science, etc. In 1954, Blick and Godt synthesized the important building block *N,N’*-dimethyl-6-amino uracil from a mixture of DMU, cyanoacetic acid, and acetic anhydride with exclusion of moisture under stirring at 60 °C for 3 h. It is a very important starting material for the synthesis of pyrimidine derivatives.

**Preparation**

DMU can be prepared by the reaction of methylamine with carbon dioxide (Scheme 1). In 1939, Grinberg reported the first synthesis of alkyl-substituted carbamides by reaction between *NO₂CONHNO₂* and methyamine. Shigeru and co-workers introduced an easy and reliable method in 1978 by treating methyamine with carbon dioxide at −30 to −50 °C for 24 h, followed by heating at an average rate of 3 °C/min in an autoclave.

**Abstracts**

(A) The synthesis of 4-aryl-3,4-dihydropyrimidines (Biginelli compounds, DHPMS) is accomplished by heating a solvent-free mixture of an aldehyde, an active methylene compound, DMU, and Dowex-50W ion-exchange resin.

(B) The simple heating of two equivalents of phenyl acetaldehyde with DMU in the presence of *BF₃·OEt₂* (10 mol%) as a catalyst in toluene afforded dihydropyrimidinone in 92% yield.

(C) The reaction between *o*-bromo benzoate and DMU in the presence of Xantphos as the initial ligand and the weak base Cs₂CO₃ provided the quinazolinedione in 90% yield.

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**Scheme 1**

MeNH₂ + CO₂ → MeNHCO₂NH₃Me

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(D) The interaction of 1,3-dimethylbarbituric acid, glyoxals, and DMU in methanol with a catalytic amount of glacial acetic acid led to 5-(5-aryl-1,3-dimethyl-2-oxo-2,3-dihydro-1H-imidazol-4-yl)-1,3-dimethylpyrimidine-2,4,6-triones.  

\[
\begin{align*}
\text{Me} & \quad \text{H} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

(E) N-methyl imines can be synthesized by the reaction of DMU and aldehydes in the presence of solid clay-montmorillonite K10.  

\[
\text{MeHN} - \text{NHMe} + \text{RCHO} \xrightarrow{\text{montmorillonite K10}} \text{RHC=NMe}
\]

(F) The regioisomeric diene DMU 1,2-adducts A/B were synthesized by reacting isoprene with DMU using palladium(II) catalyst (O2/cat.) (method A). Switching from oxygen to benzoquinone as reoxidant avoids the generation of water and affords 1,2-adducts A/B in good yield (method B).  

\[
\begin{align*}
\text{MeHN} & \quad \text{NHMe} \\
\text{O} & \quad \text{(1.2 equiv)} \\
\text{MeHN} & \quad \text{NHMe}
\end{align*}
\]

(G) The conversion of benzylamine into the triazone derivative was achieved by reflux condensation with DMU and aqueous formaldehyde under argon atmosphere and heating at 100 °C for 16 h.  

\[
\text{MeHN} - \text{NHMe} \xrightarrow{\text{HCHO \quad BrNH2 \quad 100 °C \quad 16 h}} \text{MeN} \quad \text{NMe}
\]

(H) The addition of DMU to a mixture of isocyanide and acid chloride gave formamidine urea salts in pure form.  

\[
\text{MeHN} - \text{NHMe} \xrightarrow{\text{R"NEC \quad THF or MeCN \quad 25 °C \quad 6-9 h}} \text{R"= CHPh, t-Bu, Cy, etc.}
\]

(I) The coupling reaction between 2-chloropyridine and DMU gives primarily the corresponding mono-coupled urea.  

\[
\text{Cl} - \text{Ph} \quad 74\% \text{ yield}
\]

(J) Kolos and co-workers synthesized 4-aryl-5-(4-hydroxy-2-oxo-2H-chromen-3-yl)-1H-imidazol-2(3H)-ones by one-pot condensation of 4-hydroxycoumarin with arylglyoxals and DMU in ethanol in the presence of a catalytic amount of acetic acid within a short time (15–50 min).  

\[
\begin{align*}
\text{R1N} & \quad \text{C} \\
\text{OH} & \quad \text{N\text{HMe}} \\
\text{R2} & \quad \text{Cl} \\
\end{align*}
\]

References

(7) Gozalishvili, L. I.; Beryozkina, T. V.; Omelchenko, I. V.; Zabatyuk, R. I.; Shishkin, O. V.; Kolos, N. N. Tetrahedron 2008, 64, 8759.